

PROJECT NARRATIVE

Current physical modeling approaches to the design of small molecule therapeutics are hindered by their inability to treat the dynamic nature of protein and ligand protonation states—elementary chemical effects involving acids and bases that give up or take on protons depending upon their environment. Recently, these effects have been identified as having the potential to play a significant role in the selective inhibition of kinases—a class of biomolecular targets of high relevance to cancer and other diseases. In this proposal, we rectify this deficiency by building a dynamic treatment of protonation states into state-of-the-art alchemical binding free energy calculations, and utilize a combined computational-experimental approach to assess the prevalence and magnitude of protonation state effects in selective kinase inhibition.